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I, JANENE PEISKER, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2004901160 for a patent by MICHAEL FRANCIS O'ROURKE as filed on 05 March 2004.

WITNESS my hand this
Sixth day of April 2005

JANENE PEISKER
TEAM LEADER EXAMINATION
SUPPORT AND SALES

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PROVISIONAL SPECIFICATION FOR THE INVENTION ENTITLED:

METHODS OF DISTINGUISHING BETWEEN VASOCONSTRICTION AND VASODILATION AS A CAUSE OF HYPOTENSION

This invention is described in the following statement:-

The present invention relates to the use of the arterial pressure waveform recorded invasively or non-invasively, to distinguish between compensatory vasoconstriction with low cardiac output on the one hand from vasodilation from more severe organ damage on the other, as a cause of hypotension in acute emergencies.

The early work of Hamilton and colleagues (Am J Physiol 1944;141:235-41) (figure 1) during World War 2 showed the differences in pressure waveforms that are seen in hypotension, and how hypotension associated with vasodilation and secondary shock was associated with damped pressure waveforms and small or absent diastolic pressure fluctuations. Subsequent work (O'Rourke MF, Am Heart J 1971;82:687-702, Nichols and O'Rourke, McDonald's Blood Flow in Arteries; Arnold, London 1998 p.170-189) (figure 2) has shown repeatedly in humans and experimental animals, that acute blood loss or fall in cardiac output from other causes is associated with amplification of the peripheral pressure wave, with prominence in the diastolic components of these waves. This was attributed to a combination of vasoconstriction, causing increased wave reflection, together with shortening of systole caused by tachycardia, such that secondary pressure waves became unusually prominent. Further studies on frequency components of the pressure and flow waveforms confirmed these explanations and raised the possibility that automatic methods could be applied to pressure waves to distinguish uncomplicated from complicated shock through identification of change in frequency components of the pressure waves as well as from change in the secondary fluctuations of the waveforms in the time domain.

According to one aspect of the invention there is provided a method for measuring (invasively or non-invasively) the arterial pressure waveform from a

peripheral artery, recording those waveforms and identifying secondary pressure waveforms.

Preferably, a series of pressure waveforms are ensemble-averaged into a single waveform to provide consistency of waveform detail. The waveforms may be subjected to harmonic analysis and the moduli of their harmonic components compared whereby a hypotensive individual can be confirmed to have the higher (second and above) greater than the first harmonic is considered as having vasoconstriction as a cause of hypotension.

Furthermore, a hypotensive individual in sinus rhythm or without significant arrhythmia is confirmed to have the lowest fundamental harmonic, at heart rate less than 120/min, dominant over all other harmonics and can be concluded as likely to have vasodilatation as the cause of hypertension.

Preferably, in the hypotensive individual, amplitude of the primary wave (peak to wave foot) is compared to amplitude of the secondary waveform (secondary peak to wave foot) and the secondary wave confirmed to have amplitude less than 25% of the initial waveform as denoting hypotension due to vasodilation whereas amplitude of the secondary waveform greater than 30% of the initial wave denotes hypotension due to vasoconstriction and acute blood loss, cardiac failure, tamponade or pulmonary embolism.

In order that the invention may be more readily understood and put into practical effect, reference will now be made to the accompanying drawings in which:-

Fig. 1 shows various pressure waveforms that are seen in hypotension,

Fig. 2 shows pressure waves recorded simultaneously in the aortic arch (lower amplitude wave) and brachial artery (higher amplitude tracing) of a human with hypotension and clinical features of peripheral vasoconstriction,

Fig. 3 shows contours of pressure waveforms in peripheral (in this case radial) artery for:

A Normal condition

B Hypotension with vasoconstriction

C Hypotension with vasodilation.

Fig. 4 shows harmonic moduli of pressure waveforms A, B, C of Fig. 3.

Fig. 5 shows the ratio of harmonic moduli (H) A, B, C of Fig. 4:

In A 1st harmonic > subsequent
but $H1/(\Sigma H2\text{-}H5)$ 0.5-1.0

In B higher harmonics dominant
$H1/(\Sigma H2\text{-}H5) \ll 0.5$

In C 1st harmonic completely dominant
$H1/(\Sigma H2\text{-}H5) \gg 1.0$.

In accordance with the invention there is provided a method for determining whether hypotension in a critically ill individual is due to vasoconstriction (denoting blood or fluid loss or acute heart failure), or to vasodilation due to sepsis or organ failure.

The pressure waveform is determined accurately in a peripheral artery - preferably radial, brachial, axillary or femoral by direct puncture or by applanation tonometry or other validated method, and ensuring there is no obstruction to arteries upstream.

These pressure waveforms are recorded preferably by synchronising from a simultaneously-recorded ECG for ensemble analysis or from use of the rising limb of the pressure waveform itself.

The amplitude of the initial pressure waveform is compared with the amplitude of the secondary diastolic pressure wave in the time domain.

Harmonic analysis of the pressure waveforms is then performed and the harmonic moduli compared.

Comparison of harmonic moduli.

Fig. 3a shows the pressure wave in a young man under normal conditions with 3b the pressure wave after blood loss associated with tachycardia, and 3c the same waves in hypotensive with system or organ failure.

Fig. 4 shows harmonic moduli under these three different conditions together with differences in amplitude of primary and secondary pressure waveforms.

Fig. 5 shows how the hypotensive state due to blood or fluid loss or acute heart failure or tamponade can be separated from the hypotensive state caused by organ failure through comparison of the harmonic components of the waves. Under normal conditions, the first harmonic component is dominant over other harmonics, but higher harmonics are well represented in the pulse waveform. In the second condition (vasoconstriction) the second and higher harmonics are dominant over the first, whereas in the last condition (organ failure with vasodilation) the first harmonic at heart rate frequency is utterly dominant over all others.

Various modifications may be made in details of the method without departing from the scope and ambit of the invention.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for measuring the arterial pressure waveform invasively or non-invasively from a peripheral artery, wherein the waveforms are accurately recorded and secondary pressure waveforms are identified.

2. A method according to claim 1 wherein a series of pressure waveforms are ensemble-averaged into a single waveform to provide consistency of waveform detail.

3. A method according to any one of claim 1 or claim 2 wherein the waveforms are subjected to harmonic analysis and moduli of their harmonic components are compared.

4. A method according to any one of claims 1 to 3 wherein a hypotensive individual is confirmed to have the higher (second and above) greater than the first harmonic can be considered as having vasoconstriction as a cause of hypotension.

5. A method according to any one of claims 1 to 4 wherein a hypotensive individual in sinus rhythm or without significant arrhythmia is confirmed to have the lowest fundamental harmonic, at heart rate less than 120/min, dominant over all other harmonics and can be concluded as likely to have vasodilatation as the cause of hypertension.

6. A method according to any one of claims 1 to 5 wherein, in the hypotensive individual, amplitude of the primary wave (peak to wave

foot) is compared to amplitude of the secondary waveform (secondary peak to wave foot) and the secondary wave confirmed to have amplitude less than 25% of the initial waveform as denoting hypotension due to vasodilation whereas amplitude of the secondary waveform greater than 30% of the initial wave denotes hypotension due to vasoconstriction and acute blood loss, cardiac failure, tamponade or pulmonary embolism.

7. A method of distinguishing between vasoconstriction and vasodilation as a cause of hypertension substantially as hereinbefore described with reference to Figs. 3 to 5 of the accompanying drawings.

Dated this 5 day of March 2004

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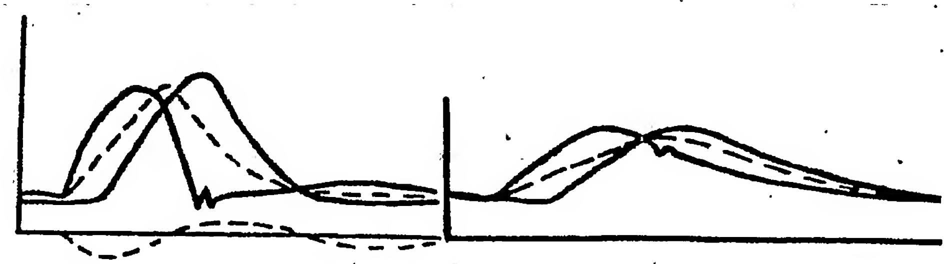


Fig. 1

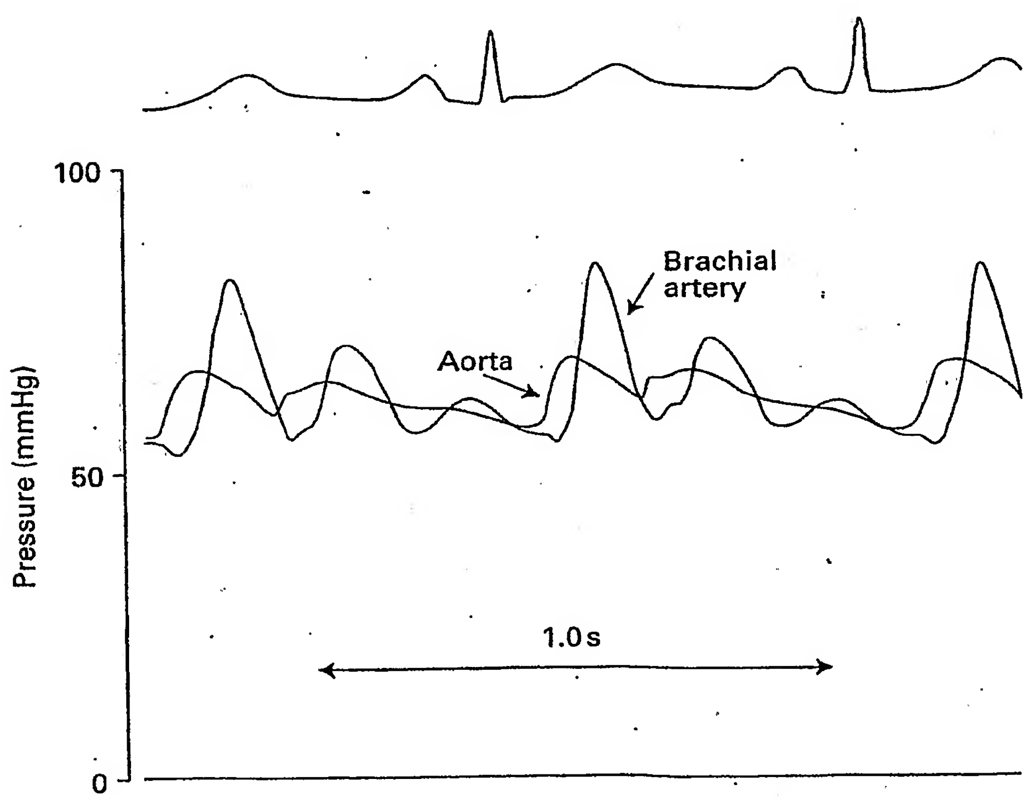
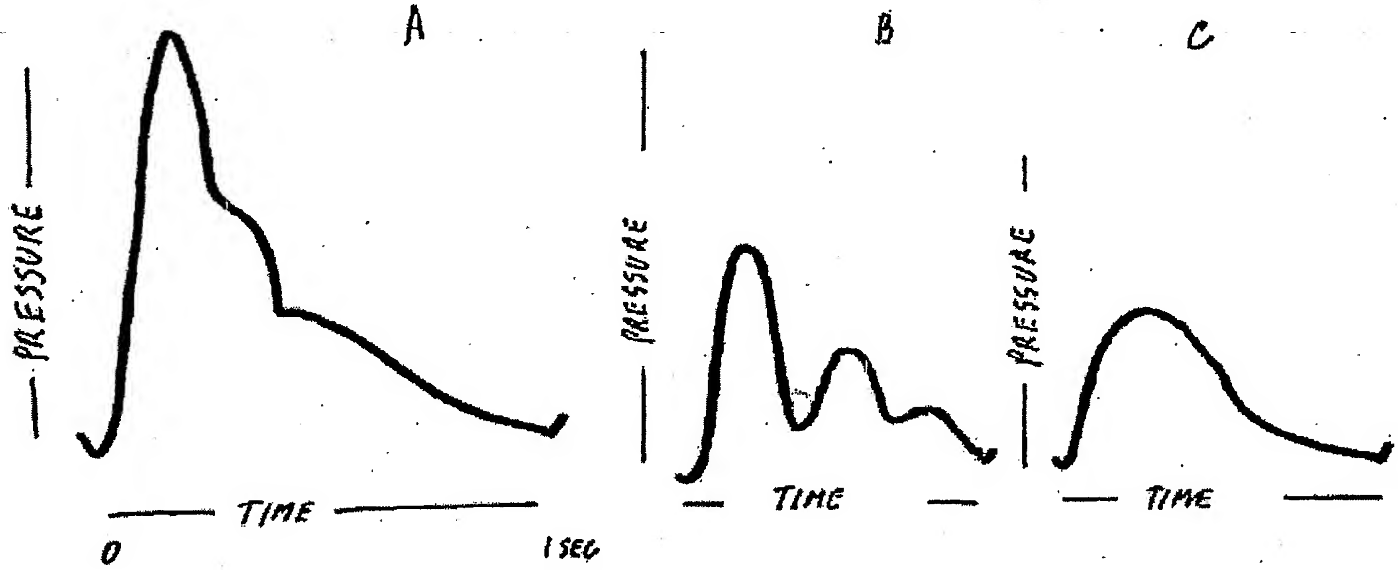


FIG. 2

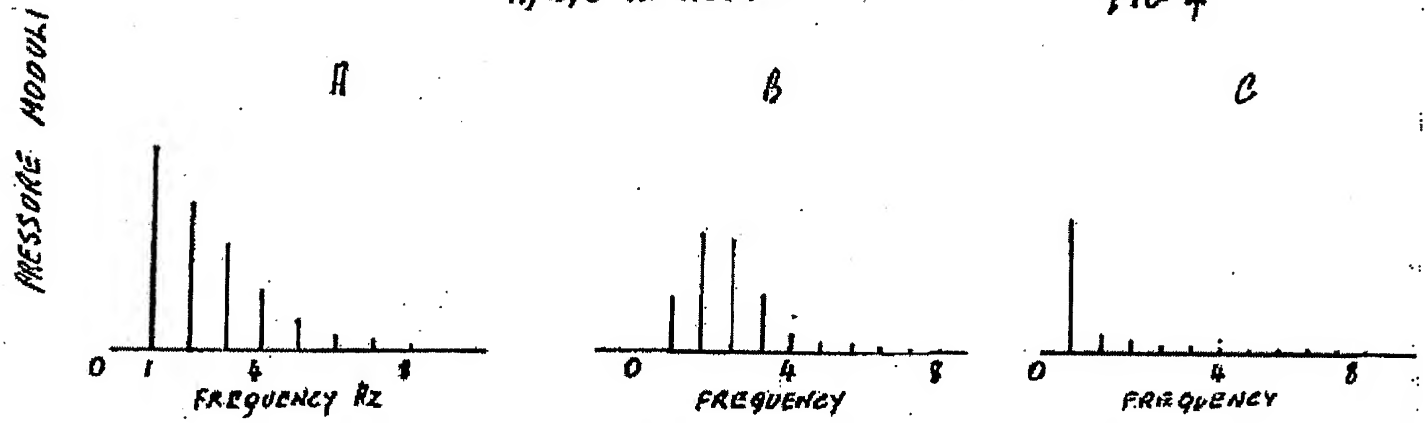
PRESSURE WAVEFORMS PERIPHERAL ARTERY
A. NORMAL B VASOCONSTRICTION
C VASODILATION

FIG 3



PRESSURE HARMONIC MODULI
A, B, C AS ABOVE

FIG 4



RATIO OF PRESSURE HARMONICS
A, B, C AS ABOVE

FIG 5